

SYNTHESIS OF SOME
4-SUBSTITUTED QUINOLINES

BY

PETER KOVACIC

A. B., Hanover College, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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INTRODUCTION

During recent years, a large number of substituted 4-dialkylaminoalkylaminoquinolines have been synthesized and tested for antimalarial activity. One of them, 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline, has been found especially effective as a therapeutic agent. In the search for an improved drug, a number of analogs were prepared.

The present work was undertaken to provide samples of four such 4-dialkylaminoalkylaminoquinolines, namely, those carrying as a substituent the fluorine atom in the 5-, 6-, and 7-positions and that carrying a methoxyl group in the 6-position in addition to a chlorine atom in the 7-position. 4-Chloro-5-cyanoquinoline and 4-chloro-7-cyanoquinoline were synthesized with the aim of eventually converting them to quinolines desirable for testing against malaria.

DISCUSSION OF RESULTS

The method of Price and Roberts (1) was used for the synthesis of 6-fluoro-4-(3-diethylaminopropylamino)quinoline. Treatment of *p*-fluoroaniline with ethoxymethylene-malonic ester gave an anil which was converted by cyclization to 3-carbethoxy-6-fluoro-4-hydroxyquinoline. Subsequent hydrolysis and decarboxylation resulted in the formation of 6-fluoro-4-hydroxyquinoline. 4-Chloro-6-fluoroquinoline was formed by treatment of the hydroxyquinoline with phosphorus oxychloride and phosphorus pentachloride and was then coupled with 3-diethylaminopropylamine.

In a similar manner, 4,7-dichloro-6-methoxyquinoline was synthesized from 3-chloro-4-methoxyaniline. The new side-chain, 1-ethyl-4-aminopiperidine (2), was introduced to give 7-chloro-4-(1-ethyl-4-piperidylamino)-6-methoxyquinoline.

In the Price-Roberts synthesis with *m*-fluoroaniline, a mixture of isomers was obtained. A separation could be

effected by recrystallization of the hydroxyquinolines from water. The more insoluble isomer was designated as 7-fluoro-4-hydroxyquinoline because of its analogy to 7-chloro-4-hydroxyquinoline. 7-Fluoro-4-(4-diethylamino-1-methylbutylamino)quinoline was then prepared in the usual manner. The reaction of 4-chloro-7-fluoroquinoline with 1-diethylamino-4-aminopentane yielded a high-boiling by-product which was believed to be 4,7-*bis*-(4-diethylamino-1-methylbutylamino)quinoline.

Price and Bullitt (3) had synthesized 7-amino-4-hydroxyquinoline by decarboxylation of 7-amino-3-carboxy-4-hydroxyquinoline, which was prepared from *m*-nitroaniline by a modification of the method of Price and Roberts. The structure of 7-amino-4-hydroxyquinoline was proved by conversion to 7-chloro-4-hydroxyquinoline which was identical with the authentic material. The introduction of the 7-cyano group into 7-amino-4-hydroxyquinoline could be effected only in low yield by a Sandmeyer reaction; the occurrence of tautomerization in the 4-hydroxyquinoline could account for the difficulties involved in diazotization. 4-Chloro-7-cyanoquinoline was prepared from 4-hydroxy-7-cyanoquinoline by the action of phosphorus oxychloride and phosphorus pentachloride.

When the Price-Roberts synthesis was applied to *m*-aminobenzonitrile, 4-chloro-5-cyanoquinoline was obtained. The mixture melting point with authentic 4-chloro-7-cyanoquinoline showed a marked depression. Reduction in the presence of palladium-charcoal catalyst yielded a compound whose melting point agrees with that reported (4) for 5-cyanoquinoline. None of the 7-isomer was detected.

The antimalarial activities of the above 4-dialkylaminoalkylaminoquinolines will appear in a forthcoming monograph.

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VITA

The author was born in Wylandville, Pennsylvania, on August 1, 1921. He attended the public elementary schools in Washington and Allegheny Counties, Pennsylvania, and was graduated from Cecil Township High School in 1939. He entered Hanover College in the fall of the same year, receiving the A. B. degree in June, 1943. He enrolled in the Graduate School of the University of Illinois in September, 1943, and held a teaching assistantship from July, 1943, until June, 1944. From that time until March, 1946, he has been a Special Research Assistant in Chemistry for the Office of Scientific Research and Development. He held a University Fellowship from March, 1946, until June, 1946.



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